Remedies Needed to Address the Pathology in Reporting Adverse Reactions and Food and Drug Administration Use of Reports

The articles in this issue concerning adverse events and errors provide an overview of the anatomy and physiology of the process of soliciting and analyzing adverse drug reaction reports at the Food and Drug Administartion (FDA)[1] and a useful taxonomy of the ways of measuring errors and adverse events more generally in health care.[2] Both fall short, however, of addressing the most serious pathology and proposing adequate remedies.

INCREASING ADVERSE DRUG REACTION REPORTING

It is clear that if the reporting of adverse drug reactions to the FDA rose from the current estimated 10% of all that occur to 20%, it would take half as long to accumulate the number of reports of deaths or injuries necessary for a postapproval decision to ban or put a boxed warning on a drug, thus sparing the lives and health of many patients harmed during the interval. Despite successful experiments by the FDA and others that have shown that such increases are possible, this concept has never been nationalized or even regionalized on an ongoing basis. In Rhode Island, for example, an FDA-funded project in the 1980s resulted in a 17-fold increase in adverse reaction reports submitted annually from Rhode Island to the FDA compared with the yearly average before the project. Similar increases were not experienced nationally.[3] Without the continuation of the intervention, the reporting rate dropped back down. In the 1960s, the FDA paid residency programs a modest fee ($25 dollars) for each adverse reaction report submitted by a resident to the agency, a far preferable, public health–derived way of funding residents' activities than the "free lunches" from drug companies now so much a way of life.

Also omitted is a discussion of the inadequate feedback to the reporting physicians or pharmacists. The FDA would surely engender better will and increase the likelihood of future additional reports from the small fraction of physicians who do take the time to report adverse drug reactions if the agency would inform the reporters about other similar adverse reactions submitted for the drug and, after a more thorough review of the problem, of action taken by the agency.

PROCESSING RISK INFORMATION BY THE FDA: PRE AND POST APPROVAL

Ahmad cites 11 recent examples of drugs withdrawn because of safety reasons, actions "stimulated by adverse drug reaction (ADR) reports."[1] That the withdrawals were at least precipitated by the postmarketing ADR reports received by the FDA is not in dispute; however, what is unstated is that for at least 4 of the drugs, bromfenac (Duract), mibefradil (Posicor), troglitazone (Rezulin), and alosetron (Lotronex), clear evidence of danger existed before approval. This evidence was of the same kind that eventually led to the withdrawal, but it was not adequately heeded.[4] For an additional 4 of these drugs, terfenadine (Seldane), astemizole (Hismanal), cisapride (Propulsid), and phenylpropanolamine (PPA), there was also clear evidence of serious adverse effects long before eventual market withdrawal, similarly not acted upon until much later.

The concept of generating a signal from ADRs is useful only if the signal is taken seriously and the action taken is prompt and proportional to the strength of the signal. This is especially important when the signal confirms earlier, preapproval evidence of dangers seen in randomized controlled trials, as in the 4 drugs cited above. There has been an historic split and an imbalance of power between FDA drug review divisions and the postmarket surveillance (Office of Drug Safety) division. In too many instances, serious postmarketing safety problems identified by the Office of Drug Safety have not been acted upon because of resistance from FDA management and from the review division that originally approved the drug.

WHO OWNS THE FDA?

A recent cover story in the *British Medical Journal*, underneath a photograph of the Parklawn Building in Rockville, Maryland, where much of the FDA is located, carried the caption "Who Owns the FDA?" In several articles in that issue, the planned re-entry onto the market of Lotronex, Glaxo's previously withdrawn dangerous drug for irritable bowel syndrome, illustrates the pernicious new relationship between the FDA and the drug industry, related in part to the 1992 Prescription Drug User Fee Act (PDUFA). That Act required companies to pay fees directly to the FDA for drug regulation.[5] Richard Horton, editor of *The Lancet* wrote, also referring to alosetron, "This story reveals not only dangerous failings in a single drug's approval and review process but also the extent to which the FDA, its Center for Drug Evaluation and Research (CDER) in particular, has become the servant of industry."[6]

One of the reasons the morale in the Center for Drug Evaluation and Research (CDER) appears to be lower than in 30 years has to do with what CDER Director Dr. Woodcock has aptly described as the "sweat shop environment" created in the wake of PDUFA. In a survey by the FDA of CDER personnel in 2001, intended to find out the reasons for the high rate of staff turnover, the problems found included the following: "About one third of

respondents did not feel comfortable expressing their differing scientific opinions. . .over one third felt that decisions such as holds, refuse-to-file actions, and non-approvals are stigmatized in the agency. Over one third felt that their work has more impact on a product's labeling and marketability than it does on public health. A number of reviewers added comments stating that decisions should be based more on science and less on corporate wishes." One of the 13 recommendations in the report is to "Encourage freedom of expression of scientific opinion."[7] Unless this occurs, along with healthy debates, the FDA will not be able to attract and keep its best staff. Debate, attention to dissident views, and freedom of expression are not only the hallmarks of good science; they are also the essence of democratic governance.—**SIDNEY M. WOLFE, MD,** *Director, Public Citizen Health Research Group, Washington, DC.*

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